REMARKS

Claims 11-14, 17, 19-20, 23, 24, 26 and 27 were pending in the subject application. Applicants have canceled claims 14 and 19 without prejudice to applicants' right to pursue the subject matter of this claim in a later-filed application. Applicants have also amended claims 11, 17, 20, 23 and 24. Support for these amendments may be found inter alia in the instant specification as follows: for the term "cholinesterase" see page 29, line 16; claim 11: pages 17-18; and claim 20: page 29, lines 24-26. Applicants note that the remaining changes to the claims merely introduce minor grammatical and format changes. In making these amendments, applicants neither concede the correctness of the Examiner's rejections in the June 2, 2004 Office Action, nor abandon their right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application. These amendments do not involve any issue of new matter. Therefore, entry of these amendments is respectfully requested such that claims 11-13, 17, 20, 23-24, 26 and 27 will be pending.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 11-14, 17-20, 23, 24 and 26

The Examiner rejected claims 11-14, 17-20, 23, 24 and 26 under 35 U.S.C. §112, first paragraph, because, as stated by the Examiner, the specification, while being enabling for transgenic mice and frog tadpoles whose genome comprise a transgene comprising an AChE promoter operatively linked to a DNA sequence encoding a splice variant of human AChE expressing AChE with acetylcholinesterase activity, wherein said sequence is expressed in cells of said mouse and where

said mouse or tadpole exhibits changes in its neuromuscular function structure, and transgenic nonhuman mammals whose genome comprises a DNA sequence encoding a cholinesterase operably linked to a mammary gland promoter, where expression of the DNA sequence results in production of detectable levels of enzymatically active protein in the milk of the mammal, the specification allegedly does not provide enablement for the preparation and use of transgenic animals comprising any and all variants of said cholinesterase genes or assay systems of these animals for reasons presented in the office action mailed December 20, 2002. Thus, the Examiner concludes that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner states that the state of the art in designing transgenic animals, at the time of filing, was as a whole unpredictable, due to position effects, unidentified control elements, and other cellular mechanisms, and as such, transgenic animals must be designed "case by case without general rules" to obtain good expression of a transgene. The Examiner further states that "one could not predict whether a transgene that is expressed in a mouse (or any other animal) will also be expressed efficiently in another animal" and that this is more relevant in the instant application to claims that are broadly drawn to non-human mammals which express a recombinant DNA expression vector encoding a variety of CHE species and variants.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding

the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 14 and 19 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application.

In addition, applicants respectfully traverse the Examiner's rejection and maintain that the specification fully enables the pending claims.

Applicants note that in assessing the state of the art in the field of transgenic animals at the time of filing, one cannot rely upon references which may point at problems inherent to a particular technical aspect of this field, but rather must review and analyze a wide range of references in order to determine the state of the art.

The Examiner has cited several references which teach that generation of transgenic animals is an unpredictable art. Applicants would like to point out that contrary to the Examiner's view, the art at the time of filing in the field of transgenic animals is replete with successful case studies and thus provides both the motivation and support for practicing such methodology. Although in theory, there are a number of technical hurdles confronting one of ordinary skill in the art when designing and generating transgenic animals, the art at the time of filing provides solutions which can be used to traverse such hurdles and more importantly demonstrates that such hurdles can be easily traversed by a show of success.

Thus, contrary to the Examiner's assertion, applicants' contend that at the time of filing, transgenic animal

production, and production of recombinant proteins in the milk of such a transgenic mammal was sufficiently predictable, so as to provide one of ordinary skill in the art with a reasonable expectation of success.

Applicants wish to point out that, at the time of filing, successful production of recombinant proteins in the milk of mammals was repeatedly demonstrated for more than a decade (see, for example, early patents such as US Patent Nos. 4,873,316, 5,322,775, 5,366,894, 5,479,995, and 5,530,177). Evidence that the art as a whole, at the time of filing, did not recognize the production of transgenic animals as unpredictable, but rather as predictable, even when utilized solely as a tool for use in research, is provided in the case of Velander v. Garner, summarized hereinbelow.

US Patent No. 5,639,940 issued to Garner et al. (hereinafter "the '940 patent") disclosed a construct and protocol for production of biologically active fibrinogen in the milk of a lactating mammal. The '940 patent demonstrated only the cloning of the fibrinogen DNA sequences into a mammalian expression vector, and the expression of biologically active fibrinogen *in vitro*.

In an earlier decision, the USPTO Board of Patent Appeals and Interferences had ruled that if all of the elements of the invention (expression of recombinant fibrinogen in the milk of transgenic livestock), including the DNA, the promoters, and the experience with transgenic animals existed, there was a reasonable expectation of success in producing transgenic mammals and expressing recombinant proteins in the milk, *because the level of skill in the art was high;* that one

skilled in the art would have expected the process to be challenging, expensive, time-consuming, and tedious, but would not have expected the process to require undue experimentation; and, most importantly, that *absolute predictability is not a requirement for a reasonable expectation of success*.

The CAFC upheld the earlier decision of the Board that the success of cloning and expression of a recombinant polypeptide having biological activity recoverable from mammalian milk was not unpredictable. More specifically, the CAFC decision held that difficulty and variability are not equivalent to unpredictability, and that the level of skill in the art was high at the critical time (i.e., the time of filing, 1994):

> "The cited publications collectively indicate that, at the critical date, a person having ordinary skill in the art would have expected considerable variability in yields (including no yield), even among animals subjected to the same protocol. [That person] would have viewed such variability as an indication of the expense, time, and effort involved in producing transgenic mammals and selecting those with 'recoverable' yields, but not as an indication that success would be unlikely." (*Velander v. Garner*, Docket No 02-1366, decided Nov 5, 2003)

In other words, even when considering the complexity of the methods and potential variability of results in producing transgenic mammals, in the opinion of the Board and the CAFC, at the time these did not constitute undue experimentation for one of ordinary skill in the art.

Unlike the '940 patent of Garner et al., the instant specification provides actual proof of conception, in that it conclusively demonstrates successful production of biologically active recombinant human AChE polypeptide in the milk of lactating female transgenic mice. Certainly, by the criteria set forth in *Velander v. Garner*, the instant specification provides sufficient guidance for one of ordinary skill in the art to make and use transgenic livestock expressing human recombinant AChE or BChE.

Thus, the Examiner's assertion that successful production of recombinant human AChE or BChE in the milk of a transgenic mouse does not provide sufficient guidance for one of ordinary skill in the art to make and use other transgenic mammals expressing recombinant AChE or BChE in their milk is incorrect.

Although gene transfer into animals requires the selection of appropriate vectors, promoters and transformation methodology, the consensus in the art, at the time of filing, was that once a transgenic model system for a specific gene is generated, the construction of additional transgenic animals harboring this specific gene is a relatively straightforward task.

In fact, the predictability of model systems, in particular, the mouse model system, has led researchers to routinely use such systems to evaluate gene constructs and to thus select appropriate gene constructs and transformation methodology which can effectively and successfully be applied to larger animals of different species.

Numerous publications attribute the success of generating transgenic animals to the guidelines provided by the model system used, which is typically a mouse model system.

Since the generation of the first transgenic mice in 1980, transgene technology has also been successfully applied to a variety of animal species (see, Ebert et al. attached hereto as **Exhibit 1**), including rats, rabbits, swine (see, e.g., Brem **(Exhibit 2)**, Lo et al. **(Exhibit 3)**, Weidle et al. **(Exhibit 4)**, and Yarus et al. **(Exhibit 5)**), sheep (see, e.g., Hammer et al. **(Exhibit 6)**, Hammer et al. **(Exhibit 7)**, Simons et al. **(Exhibit 8)**, Murray **(Exhibit 9)**, Bawden et al. **(Exhibit 10)**, and Schneicke et al. **(Exhibit 11)**), goats (see, e.g., Ebert et al. **(Exhibit 12)**) and cattle (see, e.g., Krimpenfort et al. **(Exhibit 13)**, Hyttinen et al. **(Exhibit 14)**, and Cibelli et al. **(Exhibit 15)**), as well as, poultry (see, e.g., Harvey et al. **(Exhibit 16)** and Mohammed et al. **(Exhibit 17)**) and fish.

Using techniques such as DNA microinjection, researchers have been able to introduce commercially important genes into a variety of livestock animals including cattle, goats, pigs and sheep. With sufficient resources it is now possible to reliably produce transgenic animals of all commercially important species and obtain tissue and developmentally correct expression of the transgene in, for example, the mammary gland.

The production of transgenic farm animals is limited by the high costs associated with obtaining and maintaining these animals. Thus, it is prudent to confirm transgene expression in a mouse model before initiating such experiments in higher

species. Many researchers seeking to achieve transgene expression in larger mammals have understandably chosen the reliable mouse model prior to production of transgenic proteins in larger animals (see, for example, US Patent Nos. 5,366,894 and 5,633,076). Indeed, Houdebine, in an early review (J Biotechnology 1994; 34:269-87, attached hereto as **Exhibit 18**) stated that "[m]ice are routinely used to evaluate the gene constructs".

In the mouse model, less than 2 months are required to reach the stage of weaned founder pups. In contrast, verifying success in pigs can take up to a year due to a long generational interval (i.e. 114 days gestation period, 21-28 day lactation and onset of puberty at 6-9 months of age). In addition, the establishment of transgenic lines from founders can take between 1-2 years for pigs, sheep and goats and between 4-5 years for cattle. Thus, there is an obvious advantage to characterizing transgenic mouse models prior to conducting experiments in higher animal species.

In addition, generating transgenic mice models also provides researchers with valuable information since this species is well characterized with respect to transgenic experiments. In mice, differences in reproductive productivity, behavior, related husbandry requirements and responses to various experimental procedures that affect overall production efficiency are well documented (see Pinkert et al. attached hereto as **Exhibit 19**). Procedures developed for mice, such as, for example, DNA microinjection have been modified to accommodate production of other transgenic species with great success. Differences between these species and mice in the embryo quality and physical response to microinjection,

requirements for embryo culture, quantity of embryos needed for embryo transfer and pregnancy maintenance, are well documented (see **Exhibit 19**) and have been available to the skilled artisan since the early 1980s. Thus, contrary to the Examiner's statements, mouse model systems serve as an excellent test system and accurately predict success in higher animals.

Due to the rapid developments made in the field of transgenic animals over the past two decades, today this field is on the verge of fulfilling its commercial potential of providing therapeutic proteins (see Brink et al. **(Exhibit 20)**; for a most recent review, see Houdebine **(Exhibit 21)**). Once transgenic mice could be generated with relative ease via pronuclear microinjection of recombinant DNA (see Gordon et al. **(Exhibit 22)**) this technology was rapidly and easily applied to other species (see Hammer et al.) including cattle (see Krimpenfort et al. **(Exhibit 12)**).

The basic procedure for generating a transgenic animal is similar for most species. After oocyte maturation and fertilization, (linearized) DNA constructs encoding the recombinant protein of choice are injected directly into the pronucleus. Subsequently, the injected embryos are transferred to foster mothers.

Other transgene delivery systems are also utilized, with increasing efficiency:

> "The generation of transgenics has recently become easier or possible for different species thanks to the use of transposons or retrovirus, to incubation

> of sperm which DNA followed by fertilization by intracellular sperm injection or not and to the use of the cloning technique using somatic cells in which genes have been added or inactivated." (Houdebine (2002) *J. Biotechnol.* 98: 145-160).

The most promising approach is based on the use of retroviral vectors, and nuclear transfer (NT) which involves the introduction of the nucleus from a totipotent donor cell such as embryonic germ cells (EG cells), transfected with the desired gene, into a mature enucleated oocyte by electrical fusion. The introduction of foreign genes (transgenes) into EG cells is achieved by standard transfection procedures and selection of transgenic cells is based on antibiotic resistance.

Indeed, many patent publications teaching the production of recombinant polypeptides in the milk of lactating female transgenic livestock have demonstrated the stepwise proof of concept from design of the expression construct, through expression of biologically active recombinant polypeptide *in vitro,* production of the desired recombinant polypeptide in the milk of small transgenic mammals such as mice, and then adaptation of the mouse model to larger transgenic livestock animals such as cattle and goats. Examples of such stepwise proof of concept can be found in US Patent No. 5,366,894, which describes the expression of human factor IX in the milk of lactating ewes. The probability of successful transgenesis and expression in milk in the sheep was confirmed in experiments with mice:

> "This clone (SS-1) presumably contains all the

> necessary sequences to ensure high levels of expression in the mammary gland of a transgenic mouse and can thus be expected to function as efficiently, if not more so, in the homologous species i.e. in a transgenic sheep. Consequently, fusion genes derived from this clone can also be expected to express (efficiently) in the ovine mammary gland." (Example 7)

Similarly, US Patent No. 5,633,076, which teaches methods for producing transgenic bovines and for expression of transgenes in their milk, describes the evaluation of different constructs for expression of human lactoferrin first in murine milk (Example 14) and, on the basis of success in mice, expression of the recombinant human protein in bovine milk (Example 15).

Thus, the fact that the instant application provides working examples for generating transgenic mice, that transgenic mice are well accepted as an excellent model system and that the art at the time of filing the subject application provides sufficient guidance as to suitable transformation methods and constructs which can be used with various animals, clearly indicate that the instant specification enables and motivates one of ordinary skill in the art (by showing success in mice) to generate other transgenic animals without having to resort to undue trial and error experimentation.

Applicants contend that the major hurdle to generating transgenic mammals expressing AChE or BChE in the milk is not technical but rather conceptual. Once guidelines for generating transgenic animals expressing AChE or BChE (or

biologically active variants thereof) are provided by the instant specification, and success is demonstrated via the mouse model, one of ordinary skill in the art would be motivated and certainly capable of generating any transgenic animal with reasonable degree of success without having to resort to trial and error experimentation. Indeed, Karatzas et al. (US Patent Application Publication No. 2040016005), following the protocols taught in the instant specification, demonstrated the cloning and expression in milk of substantial amounts of recombinant human BChE protein. Karatzas et al. followed the same stepwise strategy as Clark et al., De Boer et al. and others, first expressing the human BChE *in vitro* in a human cell line, using the very same assays for measuring enzyme activity as those used by applicants, then evaluating expression of different constructs in murine milk and only then selecting efficiently expressed constructs for transformation and expression in transgenic goat milk.

Thus, the instant application provides all the elements necessary to enable and motivate a person of ordinary skill in the art to generate any non-human animal expressing transgenic human or insecticidal cholinesterase in any of its target tissues with probable expectation of success without undue experimentation. The specification provides a detailed description of human AChE and BChE sequences (or biologically active variants thereof), suitable promoters and the methodology resulting in successful generation of transgenic mice expressing human AChE and BChE. On the basis of successful transformation of mice, a person of ordinary skill in the art would have been able to transform other animals (e.g., goats, pigs, sheep, cows or rabbits) with human AChE and BChE sequences (or biologically active variants thereof)

at the time the invention was made without undue experimentation, as explained hereinabove.

The principle teachings of the present invention have been validated by Nexia Biotechnology Inc. which produces the human BChE in milk of farm animals. Nexia's recombinant product is described in www.nexiabiotech.com/en/01_tech/09.php:

> "Protexia™ is Nexia's recombinant version of butyrylchoinesterase (BChE), a naturally occurring protein found in minute quantities in blood. Studies in the literature have used plasma derived BChE in animal studies and have shown that increasing BChE concentrations in the blood protect laboratory animals from the toxic effects of nerve agents. BChE functions in the blood as a bioscavenger, like a sponge, to absorb the nerve agent before it can do its damage. Protexia™ will be developed to treat and prevent the toxic effects of nerve agents and other dangerous compounds."

Clearly, successful generation of transgenic farm animals as shown by Nexia confirms that the teachings of the present invention (which inspired and guided Nexia's efforts) are enabling.

Claims 11-14, 23, 26 and 27

The Examiner rejected claims 11-14, 23, 26 and 27 for allegedly lacking an enabled use for the claimed animal. The Examiner asserts that the claimed animal may be used as a model of neuromuscular junctions but it could only be useful if the expression of the transgene results in a phenotype. In

addition, the Examiner asserts that the claimed animal may be used as a bioreactor which could only be useful if the cholinesterase transgene is expressed in the mammary gland.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 14 without prejudice or disclaimer to their right to pursue the subject matter of this claim in a later-filed application.

In addition, applicants respectfully traverse the Examiner's rejection and maintain that the specification fully enables the pending claims.

As stated in the instant application, the claimed animals expressing transgenic (e.g., human) cholinesterase can be used as model systems to assay "for anti-cholinesterase substances" (page 1, lines 14-15) and, more particularly, to assay "the effects of various anti-cholinesterase substances in vivo" (page 1, lines 19-22). The present invention is particularly aimed at allowing "rapid, effective and reliable screening of anti-cholinesterase substances" (page 1, lines 19-20).

Applicants wish to point out that the Examiner is incorrect in asserting that the utility of the claimed animals as model systems is conditioned upon phenotypic effect of the expressed transgene on the animal host. In fact, all that is necessary is an expression of the transgenic cholinesterase activity (preferably in blood) of the model animal since such an expression, enables use of the transgenic animal as a test

system for anti-cholinesterase agents. Accordingly, the effect of any test substance on the transgenic cholinesterase activity can be readily determined, for example, by comparing the total serum cholinesterase activity measured in transgenic mice and in similar non-transgenic mice being exposed to the test substance. Serum cholinesterase activity in model animals can be reliably and accurately measured using analytical techniques which were well known and widely used in the art at the time the invention was made (see, for example, Harlin and Ross **(Exhibit 23)**, Landis and Carakostas **(Exhibit 24)**, and Carakostas and Landis **(Exhibit 25)**. Furthermore, measurements of serum cholinesterase activity in laboratory animals (non-transgenic) have been routinely used to evaluate the effect of anti-cholinesterase substances (see, for example, Pope et al. **(Exhibit 26)**).

Hence, a person of ordinary skill in the art would have no difficulty in using the transgenic model animal of the present invention in assays for the general use of identifying anti-cholinesterase substances.

In addition, the transgenic animals are particularly advantageous for many specific uses. The transgenic model animals of the present invention expressing human cholinesterase are particularly suitable for screening of substances which are either preferably capable of or preferably incapable of selectively inhibiting human cholinesterase activity, either for the purpose of validating anti-cholinesterase substances which are safer for human use (e.g., safer insecticides) or for the purpose of identifying agents which can reverse or prevent the effects of poisonous nerve gas agents. Accordingly, the instant application states

(on page 33, lines 23-25) that "The transgenic mice system is advantageous in that it provides *in vivo* model system which is closer to human physiology".

Another advantage of using the transgenic model animals of the present invention is that they allow evaluating substances for their specificity to a target enzyme or organism. Thus, substances can be identified for selectively inhibiting any specific human or insect cholinesterase activity while not affecting the model animal.

Other obvious advantages of using the transgenic model animals of the present invention are that they allow quantitative assessment of the anti-cholinesterase efficiency of tested substances, identifying novel substances which are antagonistic (antidotes) to known anti-cholinesterase poisonous agents (e.g., organophosphates, nerve gases) and assessment of different polypeptides for their capacity to neutralize the poisonous agents.

Hence, clearly, the transgenic animals of the present invention are highly useful and advantageous as model systems for numerous applications.

In view of the above remarks, applicants maintain that claims 11-13, 17, 20, 23, 24 and 26 are enabled as required under 35 U.S.C. §112, first paragraph. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 11-14, 17-20, 23, 24, 26 and 27 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 14 and 19 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application.

With respect to claims 11, 17, 19, 23 and 24 the Examiner points out that these claims are allegedly confusing as they state cholinesterase of ChE enzyme. In response, applicants respectfully traverse. Nevertheless, without conceding the correctness of the Examiner's rejection but to expedite prosecution of the subject application, applicants have hereinabove amended claims 11, 17, 23 and 24 by deleting the terms "ChE" and "enzyme".

Applicants also note that claim 11 has now been amended according to the Examiner's suggestion with respect to genome integration of the recombinant construct. The variants cited in claims 11, 13, 19 and 23 have now been further qualified as having cholinesterase activity thereby traversing the Examiners rejection with respect thereto.

In addition, claim 11 has been further amended to add a promoter functional in the host.

Finally, claim 17 has now been amended so as to remove any confusion with respect to the role of the promoter in the transgenic host.

In view of the above amendments and remarks, applicants maintain that claims 11-13, 17, 20, 23, 24, 26 and 27 satisfy the requirements of 35 U.S.C. §112, second paragraph. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 11 and 13 under 35 U.S.C. §102(b) as allegedly being anticipated by US Pat. No. 4,736,866 to Leder.

The Examiner asserts that Leder teaches transgenic mice comprising the myc oncogene which includes nucleotides A, T, C and G. The Examiner asserts that since the claims do not specify any characteristics of the "fragment" of SEQ ID NOs: 1, 3 or 5 any single nucleotide is a fragment and therefore anticipated by Leder.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 11 such that the fragment or variant is characterized by having cholinesterase activity.

The Examiner has rejected claims under 35 U.S.C. §102(b) as allegedly being anticipated by Velander et al. (Proc. Natl. Acad. Sci. (USA) 89: 12003-12007, 1992). The Examiner asserts that Velander et al. teach transgenic pigs expressing protein C operatively linked to a mammary gland promoter, where detectable levels of protein C are found in the milk of pigs. The Examiner asserts that protein C is an enzyme with protein cleaving activity and further asserts that protein C is regarded as having a biological activity of cholinesterase and therefore anticipates the claimed invention.

Independent claim 11 of the application clearly recites that the protein expressed by the present invention is selected from the following categories: "(a) wild-type human AChE; (b) wild-type human BChE; (c) variants of (a) and (b) having cholinesterase activity."

Clearly protein C cannot be classified under (a), (b) or (c) of claim 11 and as such, the teachings of Velander et al. cannot serve as a basis for rejection.

In addition, applicants point out that the Examiner is incorrect in asserting that protein C possesses the biological activity of cholinesterase. Velander et al. describe protein C by reference to Emson (Science 235:1348-1352, 1987, **Exhibit 27**) as follows: "Protein C is a zymogen of a serine protease that is activated by thrombin" (page 1, left column, lines 3-4 of last paragraph). Thus, in fact, protein C is an inactive enzyme (proenzyme) involved in blood clot formation which is activated specifically by thrombin and as such protein C (in the form expressed by Velander et al.) is incapable of

hydrolyzing acetylcholine into acetic acid and choline. Accordingly, Velander et al. assessed the activity of human protein C in transgenic swine according to its anticoagulant activity (see Abstract). Hence, clearly, Velander et al. do not anticipate the claimed invention.

Notwithstanding the above, applicants would like to further point out that protein C does not possess the organophosphate binding activity attributed to cholinesterases. As is detailed in the instant application such organophosphate binding activity is also a feature of the present invention since it enables use of the expressed product in neutralizing organophosphates.

In view of the above amendments and remarks, applicants maintain that the pending claims satisfy the requirements of 35 U.S.C. §102(b). Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the now pending claims, i.e. claims 11-13, 17, 20, 23-24 and 27.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $475.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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